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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,321	07/13/2001	Yousuke Takahama	31671-173265	2334

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/889,321	TAKAHAMA, YOUSUKE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 January 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): The rejection of claim 9 under 35 U.S.C. 112,second paragraph..
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-12*.
   Claim(s) withdrawn from consideration: *13-19*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached sheet..
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Attachment to Advisory Action

11. cont. Applicant's arguments do not overcome the rejection of claims 1-12 under 35 U.S.C. 103(a) as being unpatentable over Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-2647, in view of DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335, and further in view of Bakker et al. (1999) J. Immunol., Vol. 162, 3456-3462. Applicant's arguments are a reiteration of the arguments previously presented, fully considered, and not found persuasive in the final office action. Pages 3-9 of the final office mailed to applicants on 10/21/05 are presented below for applicant's convenience.

The applicant again presents arguments against each of the cited references individually and then states that even in combination the cited references do not teach the claimed invention. The applicant states that none of the cited references teach or suggest the basic technical feature of the invention, which is using immature T lymphocytes to acquire natural immunological tolerance. This is not agreed for reasons of record. As set forth in the rejection of record, the combination of the teachings of the cited references provides motivation and a reasonable expectation of success for using transfected immature T lymphocytes to induce tolerance to foreign gene products expressed from the immature T lymphocytes. It is further noted that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Furthermore, the applicant is reminded that it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In addition, it is noted that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In the instant case, Ilan et al., the primary reference, was cited for teaching the administration of cells transduced with the recombinant adenovirus into the thymus (Ilan et al., page 2640). Specifically, Ilan et al. teaches that in mammals pretreated by thymic injection of cells infected with recombinant adenovirus encoding a therapeutic gene such as human BUGT1, a second intrahepatic injection of the recombinant adenovirus resulted in sustained gene expression of at least 7 weeks (Ilan et al., page 2640). Ilan et al. further teaches that proteins other than BUGT1 can be used to generate central tolerance, such as proteins associated with autoimmune disease or allograft rejection (Ilan et al., page 2641, column 1). Thus, Ilan et al. was cited for establishing that cells containing and expressing foreign DNA can be used to induce tolerance against the foreign gene by directly administering the cells to the thymus. The applicant argues that Ilan et al. does not render the instant invention obvious because Ilan et al. only teaches the administration of hepatocytes transfected with a foreign gene into the thymus and does not teach or suggest using transfected immature T lymphocytes. However, the rejection of record is not based solely on the teachings of Ilan et al. Both DeMatteo et al. and Bakker et al. were cited to supplement the teachings of Ilan et al. The applicant then states that neither DeMatteo et al. nor Bakker et al. teach the critical feature of the instant invention, i.e. the use of immature T lymphocytes to induce tolerance, and that as none of the three references specifically teaches this limitation, the invention as claimed is not rendered obvious by any combination of the cited references. In response, the applicant is again reminded that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The office recognizes that each reference individually does not render the instant invention obvious, however, the office has established that the combined teachings of Ilan et al., DeMatteo et al., and Bakker et al. render the instant invention obvious.

The applicant further argues that since Ilan et al. does not teach the use of immature T lymphocytes to induce tolerance in the thymus that Ilan et al. does not teach the mechanism for achieving tolerance envisioned by the applicants, i.e. that tolerance is achieved through differentiation of the immature T lymphocytes in the thymus. However, applicant's conclusion that because Ilan does not teach the advantage of the alleged mechanism for tolerance induction,

Ilan cannot be used alone or in combination to demonstrate the obviousness of the invention is incorrect. The MPEP states that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991). MPEP 2144.

The motivation to modify the teachings of Ilan et al. with the teachings of DeMatteo et al. and Bakker et al., in other words the motivation to administer transduced immature T lymphocytes into the thymus to induce tolerance, is of record and is reiterated as follows. To supplement the teachings of Ilan et al., the rejection of record relies first of the teachings of DeMatteo et al. who teaches that adenovirus is capable of infecting immature T lymphocytes in neonatal thymus and further that the transduced neonatal T lymphocytes induce tolerance (DeMatteo et al., page 5330, abstract, and Figure 1). Note in particular that DeMatteo et al. teaches that it is the expression of the transgene in the neonatal T lymphocytes before maturation that induces tolerance. It was also noted in the rejection of record that DeMatteo et al. teaches that by using a cellular carrier to prevent viral extravasation into the periphery, adverse systemic reactions to adenovirus can be avoided (DeMatteo et al., page 5334, column 2). Thus, DeMatteo et al. supplements the teachings of Ilan et al. by teachings that immature T lymphocytes already present in the neonatal thymus can be transduced to express a foreign gene and that these transduced immature T lymphocytes induce tolerance. DeMatteo et al. also teaches, as does Ilan et al., that instead of directing administering the adenovirus encoding the foreign gene to the lymphocytes in the thymus, cellular carriers can be used, i.e. transduced cells. Thus, DeMatteo et al. demonstrates that cell types other than hepatocytes are useful in inducing tolerance in the thymus, and in particular demonstrates that immature T lymphocytes transduced with adenovirus induce tolerance in the thymus.

Bakker et al. was then cited to further supplement Ilan et al. and DeMatteo et al. by teaching methods of infecting immature T lymphocytes with recombinant adenovirus *in vitro* in fetal thymic organ culture (Bakker et al., page 3457). Bakker et al. was also cited for teaching that fetal thymocytes infected with adenovirus develop into single positive mature T

lymphocytes which ultimately migrate to the periphery (Bakker et al., page 3458, Figure 1, and page 3456).

As both Ilan et al. and DeMatteo et al. teach that mature T cells must be suppressed in the adult thymus in order to get tolerance induction and that cells transduced with adenovirus can be administered to the thymus to induce tolerance, and Bakker et al. teaches that immature thymocytes transduced with adenovirus develop into mature T lymphocytes and repopulate the periphery, the skilled artisan would have been motivated to administer adenovirus transduced immature T lymphocytes instead of transduced hepatocytes in the methods of Ilan et al., in order to both successfully generate tolerance to the adenovirus expressed proteins and to repopulate mature T lymphocytes in the periphery following the step of immunosuppression in the Ilan method. Therefore, in view of the need to suppress mature T cells in order to effectively achieve central tolerance by administering adenoviral infected cells to the thymus as taught by both Ilan et al. and DeMatteo et al., and further in view of the ability of transduced immature T lymphocytes to not only induce tolerance in the thymus but also to develop into mature T lymphocytes capable of populating the periphery as taught by DeMatteo et al. and Bakker et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to induce tolerance by administering transduced immature T lymphocytes into the thymus instead of transduced hepatocytes in order to both induce tolerance to the heterologous gene products expressed in the transduced immature T lymphocytes and stimulate repopulation of the periphery with mature T lymphocytes. Further, based on the successful infection of immature fetal T lymphocytes in culture taught by Bakker et al., and the art recognized ability of immature lymphocytes in the thymus to induce tolerance as taught by DeMatteo et al., the skilled artisan would have had a reasonable expectation of success in infecting immature T lymphocytes with the recombinant therapeutic adenoviruses taught by Ilan et al. and using those infected immature T lymphocytes to induce central tolerance in adult hosts following intrathymic injection.

In regards to DeMatteo et al. and Bakker et al., the applicant argues that DeMatteo et al. does not teach "fetal thymus" and that Bakker et al. does not teach that the gene transferred T lymphocytes can be used for gene transfer. In response, DeMatteo et al. teach neonatal thymus, which is similar to fetal thymus in that the T lymphocytes contained in the neonatal thymus have yet to undergo maturation (see DeMatteo et al., abstract). Thus, the T lymphocytes in the

neonatal thymus referred to in DeMatteo et al. are immature T lymphocytes. In response to applicant's arguments regarding Bakker et al., the rejection of record does not rely on Bakker et al. for teaching or suggesting the transplantation of the transduced immature fetal T lymphocytes, both Ilan et al. and DeMatteo et al., as discussed in detail above, already provide the requisite teachings and suggestion for using transduced cells to deliver foreign genes to the thymus for tolerance induction. Bakker et al. was cited for providing a reasonable expectation of success for transducing immature T lymphocytes in cell culture rather than *in vivo* as taught by DeMatteo et al. and further for providing teachings that immature fetal thymocytes infected with adenovirus develop into single positive mature T lymphocytes which can repopulate the periphery. Thus for reasons of record as discussed in detail above, applicant's arguments have not been found persuasive and the rejection of record stands.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

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